SM

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,346	03/01/2002	Allen Comer	STRATA-06949	3073

7590 07/22/2004

MEDLEN & CARROLL, LLP
Suite 350
101 Howard Street
San Francisco, CA 94105

EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,346	COMER ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6-10-04 has been entered.

Applicants' reply filed 6-10-04 has been entered. Claims 1-6 and 8 are pending and under consideration.

Information Disclosure Statement

1. The information disclosure statement filed 10-17-03 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "derived from" in claim 8 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "derived from". The specification fails to specifically define the phrase "derived from". The phrase "keratinocytes derived from a patient" means during the process of obtaining the keratinocytes from a patient, various different modifications on said kedratinocytes can happen. Those modifications encompass numerous genetic modifications, chemical modifications, and physical modifications, or their combination thereof. Therefore, the phrase "keratinocytes derived from a patient" broadly includes numerous different modifications or their combination thereof on the keratinocytes isolated from a patient. It is unclear what type(s) of modification on the keratinocyte is intended. Thus, claim 8 is rejected under 35 U.S.C. 112 second paragraph.

Applicants argue that according to the dictionary the phrase "derived from" means "to obtain from a specified source" and the "specified source" is from a "patient" in the claims (reply, p. 3-4). This is not found persuasive because of the reasons set forth above.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pre-graft human skin equivalent having a surface electrical capacitance (SEC) of 40-240pf or 80-120pf in vitro, wherein said human skin equivalent is produced by using Near Diploid Immortalized Keratinocyte (NIKS) cells, does not

reasonably provide enablement for a composition comprising a pre-graft human skin equivalent having a SEC of 40-240pf or 80-120pf in vitro, wherein said human skin equivalent is produced by using any human primary or immortalized keratinocytes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-5 and 8 are directed to a composition comprising a pre-graft human skin equivalent having a surface electrical capacitance (SEC) of from about 40-240 picofarads (pf) or 80-120pf measured as the difference in reading over a 10 second interval, wherein the skin equivalent comprises primary karatinocytes or immortalized karatinocytes. Claim 3 specifies the combined content of ceramides 5-7 in said skin equivalent is from about 20 to about 50% of total ceramide content. Claim 4 specifies the content of ceramide 2 in said pre-graft skin equivalent is from about 10 to about 40% of total ceramide content.

The specification grows NIKS cells on the dermal equivalents prepared within a 10mm MILLICELL insert with optimal media or sub-optimal media, and shows that higher total ceramide content of the skin culture was obtained when the cells were grown in optimal media as compared to sub-optimal media. Dr. Comer's declaration filed 12-23-03 shows the human skin equivalent using NIKS cells has SEC values that were between 40 and 240 pf or between 80 and 12 pf. The claims encompass a composition comprising a pre-graft human skin equivalent having a SEC of 40-240pf or 80-120pf, wherein the pre-graft human skin equivalent is produced by using any type of human primary keratinocytes or any immortalized keratinocytes.

The specification fails to provide adequate guidance and evidence for how to prepare a pre-graft human skin equivalent by using any type of human primary keratinocytes or any

immortalized keratinocytes and said pre-graft human skin equivalent has a SEC of 40-240pf or 80-120pf in vitro. Ponec et al., 1997 (Journal of Investigative Dermatology, Vol. 109, No. 3, p. 348-355) reports that "[a]lthough in recent years various human skin recombinants have been developed that show a close resemblance with native epidermis, their SC barrier function is impaired ...content of glucosylceramides, ceramides, and free fatty acid is much lower than that of native tissue...the main differences being the very low content of ceramides 6 and 7, which represents a dominant ceramide fraction... At present it is unclear whether the observed divergences in lipid profile may explain the impaired organization of the SC lipids as observed in electron microscopic... and X-ray diffraction." (e.g. p. 348, introduction). Boyce et al., 2002 (Journal of Investigative Dermatology, Vol. 118, No. 4, p. 565-572) points out that "no skin substitutes have the anatomy and physiology of native skin " (e.g. abstract), and "[f]ailure to form a barrier may be assumed to be caused by error in keratinocyte metabolism in the parthways of carbohydrate to lipid, particularly in the formation of complex ceramides. Critical to the formation of barrier lipids is the esterification of ceramides with essential fatty acids in the pathway to synthesis of acyl-glucosyl-ceramides." (e.g. p. 565, right column). Figure 5A shows that the epidermal barrier has more than 3000 SEC value at incubation day 7, however, the epidermal barrier only has SEC value of less than about 100 from incubation day 12 to incubation day 28. It seems that an epidermal barrier has much higher SEC value than native human skin early in incubation but the SEC value of the epidermal barrier depends on at what incubation time the SEC value is measured. Formation of complex ceramides in the pathway of carbohydrate to lipid in keratinocyte metabolism also plays an important role in forming skin substitute. The specification fails to provide adequate guidance and evidence for how to use

primary human keratinocytes or immortalized keratinocytes other than NIKS cells to produce a pre-graft human skin substitute which has a SEC of 40-240pf or 80-120pf in vitro.

Further, Boyce et al., 1996, (Journal of Investigative Dermatology, Vol. 107, No. 1, p. 82-87) discloses that SEC of a cultured skin substitutes (CSS) fluctuates in vitro and its SEC values are much higher than native murine or human skin. SEC of CSS in vitro shows time-dependent decrease from 4721 pf on day 3 to 394 pf on day 14 and subsequent increase to 1677 pf on day 21. After grafting, SEC of CSS decreases from 910 pf at 2 wk to 40 pf at 4 wk with no significant decrease thereafter (e.g. abstract, p. 83, right column). Goretsky et al., 1995, (Wound Repair and Regeneration, Vol. 3, No. 4, pp. 419-425) discloses that SEC of CSS before grafting in vivo is much higher than SEC of CSS after grafting and the SECs of the CSS on postoperative days 12, 14, 21 and 28 are 129, 200, 88 and 74 (+- deviations) pfs, which are comparable to the native skin. It appears that CSS or human skin equivalent in vitro has much higher SEC values and less barrier function as compared to native skins, i.e. CSS and human skin equivalent in vitro has SEC in the range of thousands of pf instead of 40-240 pf as observed in native skins. SEC of CSS or human skin equivalent decreases only after grafting in vivo where its structure is reconstituted. The state of the prior art shows that the stratum corneum (SC) function of the known human skin equivalents is impaired as compared to native epidermis, and cultured skin substitute (CSS) or human skin equivalent in vitro has much higher SEC values, i.e. in the range of thousands of pf instead of 40-240 pf as observed in native skins, and less barrier function as compared to native skins. Therefore, it was unpredictable at the time of the invention for how to make a pre-graft human skin equivalent having a SEC of 40-240pf or 80-120pf by using any type of human primary keratinocytes or any immortalized keratinocytes. In view of the state of the

art as discussed above and the lack of guidance and evidence in the present application, one skilled in the art at the time of the invention would not know how to prepare a pre-graft human skin equivalent having the claimed SEC values by using any primary human keratinocytes or immnortalized keratinocytes other than NIKS cells in vitro.

Thus, one skilled in the art at the time of the invention would have to engaged in undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

Claims 1-5 and 8 are rejected. Claim 6 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.